REMARKS

Claims 1 and 12 are pending in the application. Claim 1 has been amended. Claims 2-11 and 13-18 have been cancelled without prejudice. Support for the amendments can be found throughout the specification. These amendments add no new matter.

Obviousness-Type Double Patenting

At pages 2-6 of the Office Action, claims 1, 5-8, and 11-17 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over (i) claims 90-109 of copending application serial number 12/158,683; (ii) claims 90-109 of copending application serial number 12/158,680; and (iii) claims 1-33 of copending application serial number 12/147,752, each in view of Okamoto et al. (1995) Cancer Immunol. and Immunother. 40:173-81 ("Okamoto"). The allegedly conflicting claims of application serial numbers 12/158,683, 12/158,680, and 12/147,752 have not been patented. For this reason, the present rejections are a provisional obviousness-type double patenting rejections. In view of the remarks presented herein, it is applicants' understanding that the provisional obviousness-type double patenting rejections are the only rejections remaining in the present application. Accordingly, the double patenting rejections should be withdrawn to permit the present application to issue as a patent. See MPEP § 804.I.B. Because none of application serial numbers 12/158,683, 12/158,680, and 12/147,752 has issued as a patent, no terminal disclaimer is required for the present application. Applicants respectfully request that the Examiner withdraw the rejection.

35 U.S.C. §112, Second Paragraph (Indefiniteness)

At page 7 of the Office Action, claims 10 and 18 were rejected as being indefinite.

Claims 10 and 18 have been cancelled without prejudice, thereby rendering moot the rejection under this heading.

35 U.S.C. §112, First Paragraph (Enablement)

At pages 7-13 of the Office Action, claims 1, 5-8, 10, and 11 were rejected as failing to satisfy the enablement requirement. According to the Office Action,

> the specification, while being enabling for a method for treating cancer, which comprises the steps of: a) providing lymphocytes obtained from sentinel lymph nodes from a human cancer patient; b) expanding the lymphocytes in vitro, wherein the lymphocytes are stimulated in vitro by the addition of a substance selected from the group consisting of IL-2, IL-12, an anti-CD3 antibody, and an anti-CD28 antibody; and c) transferring the expanded lymphocytes back into the patient.

Claims 5-8, 10, and 11 have been cancelled without prejudice, thereby obviating their rejection.

Amended independent claim 1 is directed to a method for treating cancer, comprising a step of expanding lymphocytes *in vitro*, wherein the lymphocytes are stimulated with IL-2, IL-12, an anti-CD3 antibody, or an anti-CD28 antibody. As detailed in the passage from the Office Action reproduced above, the Examiner has acknowledged the enablement of the claimed method wherein the lymphocytes are stimulated *in vitro* with IL-2, IL-12, an anti-CD3 antibody, or an anti-CD28 antibody Accordingly, applicants request that the Examiner withdraw the rejection of claim 1.

35 U.S.C. §102 (Anticipation)

At pages 13-14 of the Office Action, claims 1, 5-8, and 11-17 were rejected as anticipated by Meijer et al. (2001) J. Clin. Pharmacol. 441:81S-94S ("Meijer").

Claims 5-8, 11, and 13-18 have been cancelled without prejudice, thereby obviating their rejection.

Applicants respectfully traverse the rejection of claims 1 and 12 in view of the claim amendments and the following remarks.

Meijer does not disclose exposing lymphocytes to an additional activation signal that takes place *in vitro*. Furthermore, Meijer discloses (at page 87S, 2nd half of right column) that the lymphocytes are adoptively transferred back to the patient *together with systemic administration of IL-2*. This differs from the claimed methods, as the resulting expanded

T-lymphocytes according to claimed invention effect local and site specific/directed administration of IL-2 to the tumour. It is well known in the field of cancer therapy that systemic administration of IL-2 to a patient is strongly associated with severe adverse events. According to Meijer (page 86S, left column bottom of page), the use of anti-CD3 is mentioned as a method to be used to *avoid* the use of autologous tumour cells. It is further known in the field of cell biology/immunology that the use of anti-CD3 *alone*, leads to non-specific proliferation of T-cells, which is the exact opposite with the aim of present invention, wherein it the lymphocytes are specifically tailored to attack a specific cell type. Amended claim 1 specifies that the expansion takes place *in vitro* by exposure of the lymphocytes to autologous tumour extracts. Meijer merely discloses exposure of autologous tumour extracts *in vivo* (Fig. 2 on page 87S in Meijer).

In view of the claim amendments and the foregoing remarks, applicants respectfully submit that Meijer does not anticipate claim 1 or 12. Applicants respectfully request that the Examiner withdraw the rejection.

35 U.S.C. § 103(a) (Obviousness)

At pages 15-17 of the Office Action, claims 1, 5-8, and 11-17 were rejected as being unpatentable over Chin et al. (2002) Annals of Surgical Oncology 9(1):94-103 ("Chin") in view of Okamoto, in further view of Santin et al. (2000) Am. J. Obstetric Gynecol. 183:601-09 ("Santin"), and in further view of Kan et al. (1994) Biotherapy 6:245-50 ("Kan").

Claims 5-8, 11, and 13-18 have been cancelled without prejudice, thereby obviating their rejection.

Applicants respectfully traverse the rejection of claims 1 and 12 in view of the claim amendments and the following remarks.

As acknowledged by the Examiner, Chin does not disclose sentinel lymph nodes from a human cancer patient or using autologous tumour extracts or antigen presenting cells to stimulate lymphocytes. However, it is also important to appreciate that Chin discloses a method for *in vitro* stimulation of cryopreserved lymphocytes with protein kinase C activator bryostatin-1 and ionomycin (a cytokine). Chin further describes a method wherein so-called "vaccine draining lymph nodes" are used. Even though Chin uses the term "sentinel node mapping," the way the

lymph nodes are selected in Chin *et al.* ***cannot*** be regarded as the *sentinel* lymph nodes as defined in the present application.

As detailed in the present application, "sentinel lymph nodes" are defined as the first lymph nodes in the lymphatic system that receive lymphatic drainage from a primary tumor area (see specification at page 5, lines 10-11; emphasis added). The tumour must be present at specific sites of the body and the lymph system must have developed a specific drainage of ***that*** tumour. The sentinel lymph node(s) are identified by application of a tracer substance (such as *e.g.* a dye) to the *primary* tumour area and the lymph node(s) coloured first or most intense is the sentinel lymph node(s).

In contrast, the mice used in Chin were inoculated with tumor cells lines. As a result of the use of inoculated tumor cell lines, Chin's mice did not have any primary tumors. Due to the lack of primary tumors in the mouse model system of Chin, it necessarily follows that the lymphocytes derived from these mice could not have been derived from sentinel lymph nodes, as is required by the claims. Consequently, once a dye is injected into the mice in Chin at the same injection site as the tumour cells, the dye will be transported along the same path as the tumour cells, and any lymph nodes identified will be the lymph nodes the tumour cells have been transported to or through. However, even if these lymph nodes are identified with what Chin refers to as a "sentinel node mapping method," the lymph nodes are nonetheless not "sentinel lymph nodes" as the term is used in the present application. The use of the term "sentinel node mapping" in Chin merely indicates a ***method to identify the path*** the injected tumour cells (*i.e.* cells not originating from a primary tumour within the body) have travelled in the mice and, accordingly, only those lymph nodes that have been exposed to the tumour cells on their way from the injection site to the tumour site are identified.

Conclusively, the lymph nodes identified in Chin are ***not*** sentinel lymph nodes according to the definition of present patent application.

Similar to Chin, Okamoto uses mice that were subcutaneously inoculated in the abdomen with either B16 (melanoma) or MCA (fibrosarcoma) and draining lymph nodes were harvested on day 12 or 15 (page 174, right column, 1st paragraph top of page in Okamoto). In this respect it should be noted that there is ***no mention whatsoever*** of identifying the ***first*** lymph nodes that receive drainage from the tumour. Simply collecting the lymph nodes that drain the tumour

means that a lot of collected lymphocytes are *not* lymphocytes originating from *sentinel* lymph nodes. The method of Okamoto thus resembles, at least in part, the method of Chin.

The inventors of present invention have surprisingly found that by first identifying the lymph nodes that are the *first* to receive draining from tumour (sentinel lymph nodes) and extracting the lymphocytes from these lymph nodes yields a better treatment than what has been earlier known. There is no mention in Okamoto that sentinel lymph nodes even exist, let alone that these are of importance to identify and use to extract lymphocytes for further culture and use in therapy. It should also be noted that Okamoto's culturing method does not include the use of autologous tumour extracts, as it is clearly stated in Okamoto that tumour-draining lymph node cells were co-cultured with LPS blasts (lipopolysaccharide activated B-cells; page 174, right column, 2nd paragraph) where the LPS blasts are *originating from other mice* (page 174, left column, last paragraph). Consequently, these tumour extracts are not autologous as they are originating from another individual.

Santin relates to the use of peripheral blood lymphocytes (as can be seen on page 603, left column last paragraph on the bottom of the page), which are stimulated and cultured with tumour lysate-pulsed autologous dendritic cells after which CD8+ cells were separated. It should be noted that after separation of the CD8+ cells, these cells are further expanded (page 603, right column, top of page) with autologous or allogenic peripheral blood lymphocytes. Clearly, there is no mention in Santin of any sentinel lymph nodes and no mention of any suggestion that the methods of Santin could be applied in any other context than using peripheral blood lymphocytes. There is no suggestion to a person skilled in the art to contemplate using sentinel lymph nodes at all.

Kan relates to a combination therapy using OK-432 (a streptococcal preparation) together with autologous T-cells cultured with tumour extracts and interleukin-2(3). The lymphocytes were prepared from peritoneal or pleural effusions, lymph nodes, or peripheral blood (page 246, right column, 2nd paragraph). However, there is no mention of any lymph nodes first receiving lymphatic drainage from the tumour and no mention that lymphocytes extracted from sentinel lymph nodes would be advantageous for further expansion and use in treatment. In fact it is not all discussed or suggested which one of the sources of T-cells (peritoneal or pleural effusions, lymph nodes or peripheral blood) result in the best treatment and as such there is no guidance

that even lymph node lymphocytes would be a good starting point and absolutely no suggestion to a person skilled in the art that sentinel lymph node lymphocytes would be the most advantageous starting point.

A person skilled in the art would not have found any guidance from the cited references to use lymphocytes obtained from sentinel lymph nodes in the manner claimed by the present application. In fact, none of the cited references even mention the existence of sentinel lymph nodes or their importance in adoptive immunotherapy. Consequently, the combination of the cited references fails to render obvious the methods of claims 1 and 12. As a result, applicants request that the Examiner withdraw the rejection.

At pages 17-18 of the Office Action, claims 10 and 18 were rejected as being unpatentable over WO 2001/005433 in view of Chin and in further view of Stratagene Catalog.

Claims 10 and 18 have been cancelled without prejudice, thereby rendering moot the rejection under this heading.

CONCLUSIONS

Applicants submit that all grounds for rejection have been overcome, and that all claims are in condition for allowance, which action is requested.

Please apply charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 20084-0002US1.

Respectfully submitted,

Date: September 13, 2010

/Jack Brennan/
Jack Brennan
Reg. No. 47,443

Customer Number 26211
Fish & Richardson P.C.
Telephone: (212) 765-5070
Facsimile: (877) 769-7945